UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606** Master Case No. 15-2606 (RBK/JS) Hon. Robert B. Kugler, U.S.D.J. Hon. Joel Schneider, U.S.M.J.
THIS DOCUMENT RELATES TO ALL CASES	

DEFENDANTS' REPLY BRIEF IN FURTHER SUPPORT OF MOTION TO EXCLUDE TESTIMONY OF DR. SUSAN HUTFLESS

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INTRODUCTION

Rather than respond to the relevant arguments made by Defendants in their Motion to Exclude Dr. Hutfless ("Defendants' Motion"), Plaintiffs spend pages of their Opposition discussing points that Defendants never raised or contested. *See, e.g.,* Plaintiffs' Opposition, at 3-4 (two pages discussing Dr. Hutfless' qualifications – which, while significantly overstated by the plaintiffs, were not challenged); *id.* at 11, 25 (Defendants did not claim that Dr. Hutfless could not consult with other experts); *id.* at 14 (Defendants never argued that all Bradford Hill factors must be satisfied).

To the extent Plaintiffs attempted to address arguments raised in Defendants' Motion, they did so in a circular way or were simply factually incorrect in their response. *See, e.g.*, *id.* at 15 (claiming that Defendants and their experts did not "seriously attack" Dr. Hutfless's application of the Bradford-Hill factors to the evidence, when that represented the majority of Defendants' Motion); *id.* at 16 (stating that only the *Basson* study "aimed" to study enteropathy); *id.* at 18-19 (claiming that Dr. Hutfless incorporated into her Bradford-Hill analysis all data from the epidemiological studies conducted on olmesartan); *id.* at 21-23 (Defendants did not dispute that Dr. Hutfless's reliance on mechanistic articles was proper, only that she cherry-picked data from those articles while ignoring data contrary to her opinion).

Ultimately, nothing in Plaintiffs' Opposition changes the fact that Dr. Hutfless arrived at her general causation opinion by departing from the rigorous scientific methodology she claimed to use when necessary to support her litigation-driven opinions. For those reasons explained below and more fully in Defendants' Motion, Dr. Hutfless's methodology is unsound and the Court should exclude her general causation opinion in its entirety.

LEGAL ARGUMENT

A. Dr. Hutfless's general causation opinion rests on eight MedWatch reports, and Plaintiffs fail to provide any support for this being a valid methodology.

Dr. Hutfless's general causation opinion – by her own admission – rests on eight MedWatch reports. *See* Cert. in Support of Motion to Exclude Dr. Susan Hutfless ("Hutfless Cert."), Ex. A, Hutfless Rep., at 6; Cert. of Daniel B. Carroll, Esq. in Support of Reply in Support of Motion to Exclude Dr. Susan Hutfless ("Carroll Cert."), Ex. GG, Hutfless Dep. at 416:14-417:2; 419:7-421:11. While Plaintiffs claim that Dr. Hutfless relied upon other data in reaching her opinion on general causation, (*see* Plaintiffs' Opposition, at 36 n.13), her report and testimony belie that claim. For Dr. Hutfless to reach the conclusion that a "causal association" between olmesartan and sprue-like enteropathy was established in 2006 (*see* Hutfless Cert., Ex. A, Hutfless Rep., at 6), these eight MedWatch reports necessarily provide the only evidence by which she could reach such a conclusion.

None of the purported case series or epidemiological studies on which she claims to rely were published before June 2012. A number of studies published after 2012, including the 2015 *Basson* study (on which she relies), observed that general causation "remained uncertain." *See* Hutfless Cert., Ex. V, Mickael Basson, et al., Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study, Gut 2015;0:1-6; 2 doi:10.1136/gutjnl-2015-309690 ("The causality of the association remains uncertain, and its magnitude has not been determined."). Even though Dr. Hutfless's report discussed data generated after 2012, she concluded that general causation existed in 2006 based solely on these eight MedWatch reports. *See* Hutfless Cert., Ex. A, Hutfless Rep., at 6; Carroll Cert., Ex. GG, Hutfless Dep. at 416:14-417:2; 419:7-421:11.

And although Plaintiffs' argue that Dr. Hutfless based her opinions on the clinical trials. *See* Plaintiffs' Opposition, at 36 n.13. That is a misrepresentation – as Plaintiffs well know. According to Dr. Hutfless, Defendants performed 191 clinical trials on olmesartan. *See* Hutfless Cert., Ex. A, Hutfless Rep., at 23. Dr. Hutfless identified 48 publications associated with these clinical trials that reported on gastrointestinal events. *Id.* Yet Dr. Hutfless did not include in her causation analysis data from the largest randomized clinical trial, which did not find an imbalance in gastrointestinal events in patients taking olmesartan. *See* Defendants' Motion, at 33-34; Hutfless Cert., Ex. A, Hutfless Rep., at 23-24 (dismissing this

body of "negative" data as having "limitations in the trial design" that "prevented the investigation needed" to identify potential sprue-like enteropathy cases); Carroll Cert., Ex. GG, Hutfless Dep. at 351:14-354:12. In fact, she testified that evidence from the olmesartan clinical trials did not contribute to her analysis at all:

> Q. So the long and short of it, for all that explanation, is that the 191 clinical trials addressed in 227 publications, 20 of which were done for longer than one year, do not contribute to the evidence that we are discussing of whether olmesartan causes spruelike enteropathy, correct?
>
> A. Correct.

Id. at 354:1-9.

In reference to those eight MedWatch reports, Plaintiffs spend a significant amount of time describing Daiichi's "causal assessment" of those cases and how Dr. Hutfless's assessment matched that of Daiichi. Plaintiffs' Opposition, at 36-39. Plaintiffs once again miss the point. A company's assessment of an adverse event, done for the purpose of meeting FDA reporting requirements, cannot be used interchangeably for *legal causation* purposes – as Dr. Hutfless attempts to do here. *See, e.g.*, Defendants' Motion, at 14-16 (discussing limitations placed by FDA and courts on the use of adverse event data). As Defendants pointed out in their Motion, **"Causality** is **not** a prerequisite for MEDWATCH reporting; **suspicion** that a medical product may be related to a serious event is sufficient reason for a health professional to submit a MEDWATCH report." Cert. in Support of Motion to Exclude Dr. Kessler ("Kessler Cert.) Ex. C, FOOD AND DRUG ADMIN., CENTER FOR

DRUG EVALUATION AND RESEARCH, MEDWATCH CONTINUING EDUCATION ARTICLE: THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING ("*Clinical Impact of ADE Reporting*") (October 1996), https://www.fda.gov/downloads/Safety/ MedWatch/ UCM168505.pdf, at 2 (emphases in original). Attempting to bolster Dr. Hutfless's purported "scientific" assessment of these eight MedWatch reports by pointing the finger at Daiichi's regulatory assessment of these cases – and claiming that they are consistent – simply does not pass muster under *Daubert* standards. *See Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 537-38 (W.D. Pa. 2003). Last, Plaintiffs argue that the "evidence reflects that Dr. Hutfless properly considered "alternative[]" causes in assessing these MedWatch reports. Plaintiffs' Opposition, at 35-36. But Plaintiffs' Opposition makes clear that Dr. Hutfless had no involvement in assessing information pertaining to alternative causes – as they specifically cite, repeatedly, to what *Dr. Leffler* purported to do in ruling out the potential alternative causes. *Id.* at 35-37. Despite Plaintiffs' claims, Naranjo Score Assessments of these cases – which were attached to Defendants' Motion – suggest that as of October or November of 2016, Dr. Leffler's team (and thus, Dr. Hutfless) could identify potential alternative causes for *seven* of these eight MedWatch reports. *See* Hutfless Cert., Ex. P, Naranjo Score Assessments for Eight MedWatch Reports. That notwithstanding, Dr. Leffler – and ultimately, Dr. Hutfless – magically concluded by the time they served their expert reports in late

November, 2016 that no such alternative causes existed. Plaintiffs' Opposition, at 36-39. It is unclear what information was used to reach such a divergent conclusion, and Dr. Hutfless could provide none.

The issue is not that Dr. Hutfless may have consulted with Dr. Leffler on these cases. Rather, it is that she assumed – without reviewing any supporting documentation or questioning changes in Dr. Leffler's analysis – that Dr. Leffler's say-so was valid and concluded that no such alternative causes existed. *See* Carroll Cert., Ex. GG, Hutfless Dep. at 158:2-160:9. This is inconsistent with what the Third Circuit requires of scientists like Dr. Hutfless. *See In re TMI Litig.*, 193 F.3d 613, 714-16 (3d Cir. 1999) (affirming exclusion of expert opinion where the expert failed to assess the assumptions of another expert on which he relied).

B. Plaintiffs still have not answered the question of how Dr. Hutfless narrowed the set of 335 MedWatch reports to 60.

Good scientific methodology requires a clear understanding how an analysis was undertaken. Yet Defendants still have no idea how the original set of 335 MedWatch reports was, on the eve of having to produce expert reports, suddenly reduced to a much smaller cohort of 60 forms. Plaintiffs' Opposition on this point consists of little more than unsupported declarations that the 60 MedWatch reports were selected based on clearly identified terms. Plaintiffs' Opposition, at 28-31. But nothing could be less clear than the process by which Dr. Hutfless, Dr. Leffler, or Dr. Kessler narrowed down the set of 335 MedWatch reports to the 60 that Dr.

Leffler identified as sprue-like enteropathy cases.

Plaintiffs' Opposition does not address this confusion. Instead, they describe how Dr. Hutfless arrived at the set of 335 MedWatch reports (Plaintiffs' Opposition, at 29-30) and immediately transition into Dr. Hutfless's assessment of the 60 MedWatch reports (*id.* at 31). Nowhere do Plaintiffs clarify the interim steps that occurred between the identification of both sets of reports. Dr. Hutfless is unable to identify how she went from 335 to 60 MedWatch reports and, as stated in Defendants' Motion, ambiguity remains as to: (1) how Dr. Leffler's team applied the Naranjo causality scale, if at all, to the 335 forms, (2) what terms were used to pare down the 335 forms to the set of 60, and who – among Dr. Leffler and Dr. Kessler – performed that exercise, (3) why that exercise was done in the first place, and (4) why the Naranjo scale was abandoned in favor of the WHO causality framework so late in the process. Defendants' Motion, at 16-23.

Daubert requires that litigation experts derive their opinions from applying sound scientific methodology. Here, Dr. Hutfless – and Dr. Leffler and Dr. Kessler, for that matter – appear to place great importance on these 60 MedWatch reports. *Id.* at 21-22 (citing to expert reports of Drs. Hutfless, Leffler, and Kessler in which they identified the MedWatch reports and their reliance on the same). But none of these experts agree on how these forms were identified. *Id.* Dr. Leffler testified that, in early November, Dr. Kessler sent him a group of 62

MedWatch reports and requested that he review them. Dr. Leffler determined that 60 of those reports represented cases of sprue-like enteropathy, but disclaimed having any input on the selection of that initial group of 62 forms. *See* Carroll Cert., Ex. HH, Dep. of Daniel Leffler, M.D. at 197:6-198:19. Despite Dr. Hutfless's testimony that Dr. Leffler reviewed and abstracted MedWatch reports for months prior to his receipt of the 62 reports from Dr. Kessler, Dr. Leffler initially stated in his deposition that those forms were the "only MedWatch forms" he reviewed. *See* Carroll Cert., Ex. HH, Dep. of Daniel Leffler, M.D. at 198:5-16, 198:19, 199:8-18, 200:22-25; *see also id.* at 202:12-23 (testifying that he did not speak to any other expert, besides Dr. Kessler, about the smaller set of MedWatch reports).

Dr. Hutfless's reliance on the eight MedWatch reports is wholly dependent on Dr. Leffler's assessment that all eight represented cases of "olmesartan induced enteopathy." But Plaintiffs do not speak to why many of the 335 forms did not meet Dr. Leffler's criteria – because none of these experts could articulate a coherent explanation. In other words, Defendants do not know whether the 60 MedWatch reports ultimately selected are representative of the 335 initially identified by Dr. Hutfless. Without additional information about the searches and methods used to select (and narrow) these MedWatch reports, Dr. Hutfless's blind reliance on their content to sustain her general causation opinion is unreliable

under Rule 703 and *Daubert.*

C. Dr. Hutfless's opinion is inadmissible under *Daubert* because she failed to apply the Bradford-Hill factors in a consistent or appropriate manner.

Plaintiffs' Opposition cannot salvage Dr. Hutfless's unreliable application of the Bradford-Hill factors to the evidence. Defendants do not dispute that the Bradford-Hill factors are a well-accepted framework for assessing causality. *See, e.g.*, Defendants' Motion, at 28. What Defendants object to is Dr. Hutfless's failure to apply the factors consistently to evidence that would support or refute her conclusion. *See id.* at 27-39.

1. Dr. Hutfless's analysis of the "strength" of the association rejected studies that did not support her conclusion on general causation.

Plaintiffs claim that Dr. Hutfless "diligently reviewed" all of the applicable studies and imply that she gave weight to all the data. They also assert that "only the *Basson* study specifically aimed to study whether olmesartan causes enteropathy, while controlling for confounders." Plaintiffs' Opposition, at 16. This is not true.

First, a systematic review of evidence – which Dr. Hutfless claims to have done – requires a scientist to critically examine all the evidence in an objective manner and then assign appropriate weight to each piece of data. *See, e.g.*, Holger J. Schunemann, et al., *Interpreting results and drawing conclusions*, *in* Cochrane Handbook for Systematic Reviews of Interventions 359-387; 361-66 (J. Higgins &

S. Green 2008) (discussing the GRADE approach for assessing evidence). While Dr. Hutfless may have reviewed the studies identified in her report, she gave no weight to any of the epidemiological data other than the *Basson* study. *See* Defendants' Motion, at 29-35 (discussing her dismissal of the other epidemiology studies); Hutfless Cert., Ex. A, Hutfless Rep. at 25 (concluding that the *Padwal* study, despite examining gastrointestinal-related and non-infective enteritis/colitis hospital admissions to determine if they were associated with olmesartan use, "d[id] not contribute to the evidence" on general causation); Carroll Cert. Ex. GG, Hutfless Dep., 321:10-322:20 (same). To say, as Dr. Hutfless did, that studies "do not contribute to the evidence" means that the data played no role in her ultimate causation analysis.

Dr. Hutfless also decided that data from the ROADMAP study, as well as published randomized clinical trials involving olmesartan, "did not contribute to the overall evidence" because these studies were not structured to capture sprue-like enteropathy or were purportedly missing information on gastrointestinal adverse event data. *See* Hutfless Cert., Ex. A, Hutfless Rep., at 23-24; Carroll Cert., Ex. GG, Hutfless Dep. at 351:14-354:12. But, as Defendants pointed out (*see* Defendants' Motion, at 34-35), Dr. Hutfless was more than happy to rely on MedWatch reports selected for her by another expert – MedWatch reports she acknowledged were missing information and represented the lowest quality of

evidence according to sources she trusts. Carroll Cert., Ex. GG, Hutfless Dep. at 156:20-157:2, 158:2-160:9, 233:9-22, 235:9-17.

Second, the *Basson* study did not specifically study sprue-like enteropathy. Indeed, Dr. Hutfless acknowledged that the primary and secondary endpoints of the *Basson* study analyzed malabsorption and celiac disease in association with olmesartan. *See* Hutfless Cert., Ex. A, Hutfless Rep., at 27-28 (discussing *Basson* and stating that olmesartan was associated with "malabsorption and celiac disease…"); Carroll Cert., Ex. GG, Hutfless Dep. at 271:22-272:8. It did not, as Plaintiffs state, examine whether olmesartan causes enteropathy. Plaintiffs' Opposition, at 16. Furthermore, Dr. Hutfless also admitted that the *Basson* study did not control for drugs that could cause or cure enteropathy. Carroll Cert., Ex. GG, Hutfless Dep. at 262:23-263:8. Dr. Hutfless's stated reasons for disregarding any number of studies and data that did not support her conclusions – i.e., that they did not specifically examine a sprue-like enteropathy outcome and/or failed to adjust for confounders (Plaintiffs' Opposition, at 18-21) – fall flat when one considers how she embraced *Basson* despite it suffering from the same purported flaws. *See* Defendants' Motion, at 29-35 (discussing Dr. Hutfless's rejection of *Padwal, Greywoode,* and other epidemiological studies despite embracing data supportive of her conclusions with similar issues).

Finally, Plaintiffs' Opposition does not address Dr. Hutfless's failure to

explain any of the technical flaws of the *Basson* study raised by Drs. Hansen and Risch, including the study's finding of an extremely high relative risk for celiac disease. Pls.' Cert. in Support of Motion to Exclude Dr. Risch, Ex. B, Risch Expert Rep., at 11; Pls.' Cert. in Support of Motion to Exclude Dr. Hansen Ex. A, Hansen Expert Rep., at 32-33. This is despite Dr. Hutfless's admission that olmesartan does not cause celiac disease. Carroll Cert., Ex. GG, Hutfless Dep. at 246:16-247:1.

2. Dr. Hutfless cherry-picked data from the mechanistic literature involving olmesartan.

Citing to a string of case law, Plaintiffs suggest that Dr. Hutfless should be permitted to opine on the two mechanistic papers on which she relies because the "biologic plausibility" factor is subjected to a less rigorous test than others. *See* Plaintiffs' Opposition, at 21-23, citing to Federal Judicial Center, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 597-606, 605 (3d ed. 2011) ("hypotheses are sometimes accepted under this factor…"). But the Reference Manual on Scientific Manual also states that when an "observation is inconsistent with current biological knowledge, it should not be discarded, *but the observation should be confirmed before significance is attached to it*." *Id.* at 604-05 (emphasis added); *see also In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007) (excluding expert's theory of biological plausibility, stating: "While Dr. Fogel's biological theory may be exactly right, at this point it is merely plausible, not

proven, and biological possibility is not proof of causation.").

In Dr. Hutfless's case, that is exactly why her opinion is flawed. Dr. Hutfless failed to investigate the potential mechanism for olmesartan for causing enteropathy suggested by one paper (on which she relied) by reviewing a paper by the same group of authors (on which she did not rely, but claimed to have read), which reported data that suggested a contrary conclusion. *See* Defendants' Motion, at 35-37 (discussing the 2015 *de Araujo* paper – on which Dr. Hutfless claimed to rely – and the 2014 *de Araujo* paper, which was a larger study on rats that found olmesartan had an anti-inflammatory effect in the small intestine). Her decision – for no apparent reason – to ignore data offered by the same group of investigators on which she relied is the antithesis of a disciplined, objective review of the data. Plaintiffs' Opposition, at 21; *see also* Defendants' Motion, at 37-38 (explaining that the other paper on which she relied – i.e., *Marietta* – found that the evidence did not support its primary hypothesis that olmesartan could cause enteropathy by suppressing levels of TGF beta).

3. Dr. Hutfless's failure to conduct a systematic search for case reports examining a potential association between other ARBs and enteropathy – which would be relevant to the "specificity" factor – demonstrated her willingness to behave as a litigation advocate, rather than a scientist.

Rather than address Defendants' arguments on this point, Plaintiffs inexplicably finger-point at defense experts and cite to various FDA documents.

Plaintiffs' Opposition, at 23-24. But none of this has any bearing on Dr. Hutfless's failure to conduct a systematic search for adverse events involving other ARBs and enteropathy, despite her awareness that such events existed and could bear on the question of specificity. Defendants' Motion, at 38-39.

Dr. Hutfless was aware of at least one article that described a case of enteropathy in another ARB, Valsartan. *See id.* at 39, citing Hutfless Cert., Ex. CC. Plaintiffs' claims about this evidence being non-existent are unfounded. Plaintiffs' Opposition, at 24. In fact, a number of other case reports on which Dr. Hutfless purports to rely reference cases of enteropathy found in patients taking other ARBs. *See, e.g.*, Hutfless Cert., Ex. A, Hutfless Rep., at 22, citing Marthey L, et al. Olmesartan-associated enteropathy: results of a national survey. Aliment Pharmacol Ther. 2014 Nov;40(9):1103-9. doi: 10.1111/apt.12937 (discussing patient experiencing enteropathy while taking irbesartan); Schiller D, et al. Two coincident cases of easily curable 'refractory sprue'. Gut. 2015 Nov;64(11):1714, 1773. doi: 10.1136/gutjnl-2015-309210 (noting that telmisartan and irbesartan have been reported to have enteropathy effects); Schiepatti A, et al. Olmesartan associated enteropathy: new insights on the natural history? Report of two cases. Scand J Gastroenterol. 2016;51(2):152-6. doi: 10.3109/00365521.2015.1074719 ("Finally, since cases of enteropathy associated with irbesartan, valsartan, and telmisartan have been described, the possibility of a class effect of angiotensin

receptor blockers needs to be investigated.").

Yet Dr. Hutfless did not follow up with literature searches to confirm whether evidence existed to suggest that enteropathy was occurring in patients taking ARBs other than olmesartan. Instead, she stated that her report was about olmesartan only, and concluded that that the evidence fulfilled the Bradford-Hill specificity factor. Carroll Cert., Ex. GG, Hutfless Dep. at 438:120-441:13; Hutfless Cert., Ex. A, Hutfless Rep., at 8-9. Her failure to conduct these literature searches renders her methodology litigation-driven and unreliable.

CONCLUSION

For the foregoing reasons, Defendants' Motion should be granted, and the testimony of Dr. Susan Hutfless should be excluded.

Respectfully submitted,

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